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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/572,932	11/09/2006	Yusuke Nakamura	082368-007600US	5301

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EXAMINER	
PITRAK, JENNIFER S	
ART UNIT	**PAPER NUMBER**
1635	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/572,932	NAKAMURA ET AL.	
	Examiner	Art Unit	
	Jennifer Pitrak	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 March 2007*..

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-25* is/are pending in the application.

4a) Of the above claim(s) *1-14,18-20,23 and 24* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *15,16,21,22 and 25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *11/09/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election without traverse of Group XIII in the reply filed on 03/26/2007 is acknowledged. Claims 1-14, 18-20, 23, and 24 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 03/26/07. **Claims 15-17, 21, 22, and 25 are currently under examination.**

Specification

The disclosure is objected to because of the following informalities: at least at page 40, line 15, "DISUCUSSION" appears to be a misspelling. Appropriate correction is required.

The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code (see at least p. 37 lines 23 and 33; p.38, line 6; p.39, lines 3, 12, and 24-25). Applicant is required to delete the embedded hyperlinks and/or other forms of browser-executable code. See MPEP § 608.01.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the

art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 15-17, 21, and 22 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The following factors as enumerated In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), are considered when making a determination that a disclosure is not enabling: the breadth of the claims, the nature of the invention, the state of the prior art, the level of ordinary skill in the art, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples and the quantity of experimentation needed to make the invention based on the content of the disclosure.

In the instant case, the claims are to *in vivo* methods of treating and preventing disease in a subject by administering antisense or siRNAs targeting *MGC47816.*

The nature of the instantly claimed methods, comprising administration of an antisense or siRNA targeting *MGC4781* to provide a treatment effect, *in vivo*, is subject to the considerations and limitations of nucleic acid therapeutics as discussed further below. The claims are also subject to the consideration and limitations of cancer prevention as discussed further below.

The state of the art at the time of filing, relative to the enablement of the antisense therapies *in vivo*, recognizes that there is a high degree of unpredictability in

the art due to obstacles that continue, to the present day, to hinder the therapeutic application of nucleic acids *in vivo* (whole organism) including, for example, problems with delivery and target accessibility. The following references discuss the problems of nucleic acid based therapies in reference to the claimed therapeutic antisense method.

Kalota, *et al.* 2006 (Handbook of Experimental Pharmacology, v.173, pp.173-196), published years after the instant filing date, provides a review of the challenges that remain before nucleic acid therapy becomes routine in therapeutic settings and indicate that achieving an effective nucleic acid therapy requires significant trial and error. For example, according to Kalota et al., "[A] major obstacle in employing antisense nucleic acids for post-transcriptional gene silencing is the inability to readily identify hybridization accessible sites within the target mRNA," (pp. 181-2). Kalota, et al. also notes that "a significant obstacle to be overcome [in employing antisense nucleic acids for post-transcriptional gene silencing] is the delivery of antisense molecules into cells." (p. 183).

Crooke, 2004 (Annu. Rev. Med. Vol. 55, pp. 61-95) discusses the particular problems associated with target accessibility wherein he states, "Selection of sites for induction of optimal antisense activity in an RNA molecule is dependent on the terminating mechanism and influenced by the chemical class of the compound. Each RNA appears to display unique patterns of sites of sensitivity. Within the phosphorothioate oligodeoxynucleotide chemical class, antisense activity can vary from undetectable to 100% by shifting an compound by just a few bases in the RNA target (references omitted). Despite significant progress in developing general rules that help

define potentially optimal sites in RNA species, to a large extent, this remains an empirical process that must be performed for each RNA target and every new chemical class of compounds" (p. 71, 4th paragraph).

Given this unpredictability, in particular in regard to targeting and delivery of nucleic acid compounds (antisense and siRNA molecules), the skilled artisan would require specific guidance to enable the claimed methods for inhibiting expression of *MGC47816* in a subject *in vivo*, as claimed. The instant specification does not show how one skilled in the art might overcome the obstacles to providing nucleic acid therapy of the instantly claimed methods or how applicant has overcome the same general obstacles to nucleic acid therapy in the instant invention.

Furthermore, the claims are directed to treatment and prevention of cancer (HCC). Prevention is understood to mean to keep from ever occurring. The state of the prior art considers cancer to be unpreventable and recognizes that cancer is caused by many factors as described by Bochetta, *et al.* (2004, Oncogene, v.23:6484-91)(p.6490, last paragraph): "Cancer is a multifactorial event in which numerous alterations contribute to the emergence of the malignant cell... therefore, maligant tumor growth is a dynamic process in which it is difficult to identify a unique event that caused that process." Given the known difficulty in identifying the factor or factors that cause cancer, one of skill in the art would conclude that no method will prevent cancer from occurring. The instant specification provides no support for cancer prevention, and only provides evidence of inhibiting cultured cancer cells (Alexander and HepG2) *in vitro*.

Therefore, the skilled artisan would have to perform a large and undue quantity of experimentation to perform the instantly claimed methods.

With regard to the amount of direction or guidance presented, the specification as filed does not provide sufficient guidance or instruction that would teach one of skill in the art how to successfully practice the instantly claimed methods. The specification discloses examples of administration of siRNAs targeted to *MGC47816 in vitro* to cultured cells and that such administration inhibits expression of the targeted *MGC47816* (p.38). The specification, therefore, sets forth the assumption that these *in vitro* effects translate to an effect in a subject with antisense oligonucleotides and siRNAs targeting *MGC47816* but provides no evidence to support this assumption. The specification does not show or demonstrate how the *in vitro* reduction of *MGC47816* in cultured cells leads to an effect in a subject.

In regard to the amount of experimentation that would be required to enable the instantly claimed methods in their full scope, the specification does not provide sufficient and specific guidance that would enable the skilled artisan to make and use the claimed methods of treatment in their full scope, without performing a large quantity of *de novo*, trial and error experimentation. This undue, *de novo* trial and error experimentation would require, at a minimum, determining which oligonucleotide sequence or sequences inhibit(s) the expression of *MGC47816* and, subsequently, how to deliver, *in vivo*, the antisense oligonucleotide(s) or siRNA to a target cell and have the claimed effects of treating or preventing hepatocellular carcinoma. These determinations would be required to be performed to enable any method of inhibiting expression of

MGC47816 in a subject, let alone a method of treating or preventing cancer. No specific guidance is provided in the specification that would allow a determination of the appropriate and successful modes of delivery *in vivo* such that the claimed antisense or siRNA could be provided, at a significant level for a sufficient amount of time to produce an effect as claimed.

Given the unpredictability in the field of antisense, the experimentation required to enable the instantly claimed invention, commensurate with the full scope of what is claimed, would not be routine, as evidenced by the state of the art which considers that delivery to provide an *in vivo* treatment effect must be determined empirically (as set forth above). Based on the lack of specific guidance in the specification regarding the direction in which the experimentation should proceed, even if the *de novo* experiments required were considered routine by those of skill in the art (which they are not), the more or less standard nature of each experiment would be outweighed by the sheer quantity of *de novo* undue trial and error experimentation required to determine how to practice the method of the instant invention. Moreover, even through such undue experimentation, the skilled artisan would not even expect to be successful for the broad scope of treatment as claimed.

In conclusion, due to the nature of the invention as a nucleic acid therapeutic for use *in vivo*, the degree of unpredictability in the art of antisense therapy at the time the invention was made and even to the present day, the breadth of the claimed method as a method of inhibiting apoptosis-specific eIF-5A and reducing levels of any cytokine produced in a cell in a subject, the lack of disclosure of a representative number of

species of method within the broad genus of methods of treatment as claimed, the lack of specific guidance as to what particular antisense or siRNA sequences would provide a treatment effect commensurate with the full scope of what is claimed, the need to screen multiple species of the antisense oligonucleotides required by the instant methods, so as to identify additional particular species as functional and the quantity of *de novo*, trial and error experimentation necessary to discover the above, an undue amount of *de novo* trial and error experimentation would be required in order to practice the method of treatment and prevention that is now claimed.

Therefore, the inventors have not enabled one skilled in the art to make and use the methods of the claimed invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 21, 22, and 25 are rejected under 35 U.S.C. 102(e) as being anticipated by Khvorova, *et al.* (US 2007/0031844 A1, priority filing date of 09/10/2003) ("Khvorova").

The claims are to a composition for treating or preventing HCC, wherein the composition comprises a pharmaceutically effective amount of an antisense polynucleotide or siRNA against *MGC47816* as an active ingredient, and a pharmaceutically acceptable carrier and, more specifically, claim 22 is to the composition wherein the siRNA comprises a sense strand comprising a nucleotide sequence of SEQ ID NO: 19. A sense strand comprising ***a*** nucleotide sequence of SEQ ID NO: 19 can be any sense strand containing 2 consecutive nucleotides of SEQ ID NO: 19. This is distinct from a sense strand comprising ***the*** nucleotide sequence of SEQ ID NO: 19, which must contain all of SEQ ID NO: 19.

Khvorova teaches the siRNA sense strand sequence, SEQ ID NO: 1564004, which comprises a nucleotide sequence of the instant SEQ ID NO:19 as shown here.

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SEQ ID NO:19              5'-GUGUCCGCUGACAGAACAA-3'
                                  ||||||||
SEQ ID NO:1564004                 5'-CAGAACAAGGCAAGCAGTT-3'
(Khvorova)
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At paragraph [0009], p.1, Khvorova teaches that the siRNAs of their invention can be used as therapeutic agents against diseases. Thus, Khvorova clearly anticipates the instant claims 21, 22, and 25.

Closing

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer Pitrak whose telephone number is 571-270-

3061. The examiner can normally be reached on Monday-Friday, 8:30AM-5:00PM, EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Schultz can be reached on 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

JSP

/Tracy Vivlemore/
Examiner, AU 1635